Der Kassenarzt
Deutsches Ärztemagazin · Nr. 51/52 · Dezember 1987

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Probleme mit dem Passivrauchen

008969

Der Kassenarzt, (1987), 27:(51/52), pp. 29-39

(uncertified translation)

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The Problems of Passive Smoking

People are faced day and night with reports about the presence of noxious, in particular carcinogenic, substances in almost all spheres of life. They are found in our food and drink etc. just as much as in the air we breathe. Thereby the impression is created that all these substances are man-made and the result of industrialisation. In truth many of them occur throughout nature and mankind has been exposed to them since the beginning of phytogenesis. In order to survive at all in such a hostile environment, Man has over millions of years developed effective defence systems, already recognised by Paracelsus and reflected in his doctrine: "dosis facit venenum". Whether this applies to carcinogenic substances too, which would be plausible, is at present the subject of controversial discussion. There are those who are convinced that the biological defence systems only break down if they are metabolically over-loaded; there are ample examples of this. They do not believe that the simple mechanistic view is tenable according to which injury to health occurs in direct proportion to the cancerogenic substances absorbed and thus believe in the existence of a threshold in respect of these substances. In contrast, there are others who will not budge from their opinion that even one cigarette per day or one puff from a cigarette or even the fact of passive smoking will contribute to bring about cancer some decades later. This controversy will endure until we understand the molecular and cellular mechanisms which trigger off cancer in individuals -- and we are still far from that day. The following article is intended to show the present state of scientific research into the problem of passive smoking, which leads us to the conclusion that a minimal risk to health through passive smoking cannot be either excluded or proved.

The historical background

In Europe the battle of Authority against smoking goes back to the 17th century. The many prohibitions against smoking issued in almost all countries were based on a variety of reasons, but hardly ever on the grounds of it being a nuisance, let alone a possible risk to the health of non-smokers. It was left to our Federal Government to recognise, at the beginning of the seventies, "with adequate certainty that the proved injury to health through smoking can also occur through passive smoking in the same way although to a lesser degree" (Bundestag Printed Matter 7/2070). This is the more astonishing as, at that time, scientific research into passive smoking had not even begun in earnest. To what extent such an evident analogism can be used

to justify a statement of that nature was not even investigated at the time. At any rate the world of science felt called upon to pay more attention to the problem of passive smoking. In so doing it was following a world-wide trend which had been set in motion and which was being maintained by the ever more heated discussion about the risks to health through smoking. To date a vast number of papers have been published and many congresses held on the subject of passive smoking. Two original papers and two review articles stand out from the almost overwhelming mass of literature. The two original papers, of which one is scientifically without value and the other subject to a great deal of doubt, have contributed to heating up the discussion about passive smoking throughout the world, whereas the review articles, which differ greatly in quality, have done the same within the Federal Republic.

In 1980, the 'New England Journal of Medecine' published the results of a study by White and Froeb showing that chronic exposure to tobacco smoke at work brought about a significant deterioration in the lung function of non-smokers. So far as the authors were concerned, and those who wanted to believe it, this paper for the first time provided proof of the harmfulness of passive smoking. In fact, however, the results obtained by White and Froeb are not scientically tenable. Professor Lebowitz, one of the co-authors of the American Surgeon General's Report, for instance, declared the following at a hearing in Washington: "The basic problem with the White and Froeb study is that it was ill-planned from the epidemiological point of view. The difficulties are inherent in the paper from its very beginning to the statistical analysis and affect all data and the conclusions. The fact that some time between 1976/77 and the time when the study was published 3000 people were taken out of it, whereby the results suddenly became significant, is particularly remarkable. Unfortunately Dr. White cannot remember why he removed these 3000 people from his study." Following a visit to Dr. White, Professor Gostomzyk, Head of the Health Office of the city of Augsburg and Dr. Heller of the Institute for Mathematical Economic Theory of Karlsruhe University commented in a similar manner. They summarised their impressions as follows: "The working methods of Dr. White are not those of a scientist but are more like those of a layman convinced of his ideas". Quite irrespective of this shattering assessment the work fulfilled its purpose in that for the first time it rendered smokers responsible for damaging the health of their fellow-men. It enabled Dr. White who is a sports teacher and active in the Californian anti-smoking movement to influence a plebiscite in California on smoking in public places and at work. In addition it is quoted by other authors whenever the injurious effect of passive smoking on the lung function of non-smokers is emphasised. In "Berichte (Reports) 3/86" of the Federal Office for the Environment it is even regarded as the only paper of its kind which can withstand criticism. It is therefore not to be wondered at that the Council of Experts on the Environment

used it to bolster up the ideas contained in its recently completed Expert Opinion.

One year later there appeared in the 'British Medical Journal' the publication of Hirayama's further results of a cohort-study begun in 1965 on the influence of life-style and environmental factors on the origins of disease in Japan. A side-result of this study had been that non-smoking wives of smoking husbands die more frequently of lung cancer and - for whatever reason - commit suicide more often than non-smoking wives of non-smoking husbands. This study, which even today remains the most important of all the epidemiological studies undertaken into the problems of passive smoking and which has provided a new dimension for the discussion of this issue, constitutes a watershed. For some it is the final proof of the risk of cancer through passive smoking, for others it is no more than an unscientific fabrication in which figures were manipulated until they attained the desired level of significance for the dose/response ratio. Whatever may be right, the study leaves many questions open and there are hypotheses on the basis of which the findings can be explained without reference to passive smoking. The real scandal however is that Dr. Hirayama is neither willing nor can be forced to lay his original data open for examination. Only a few weeks ago he answered with a smile an invitation to do so at a Tokyo symposium.

In 1985 the Senate Commission of Enquiry into Substances Noxious to Health included passive smoking in the MAK-List. In a detailed statement of motive, it endeavoured to justify its suspicion of passive smoking as being carcinogenic. In so doing the Senate Commission was aware of the fact that the causal link betwen passive smoking and lung cancer is the subject of controversial discussion and that the available epidemiological findings can at best indicate a serious hypothesis. According to its principles, carcinogenic substances should if possible be wholly shunned at work or, where this is not possible, they should be kept as low as possible, since the Commission does not assume there to be threshold values for these substances. Because tobacco smoke contains mutagenic and carcinogenic substances the Commission considers the inclusion of passive smoking in the MAK-List to be obligatory and it even feels that this would have been possible many years ago. It does, however, seem doubtful whether any relevant statement concerning dangers to health through passive smoking can be made on this basis without it being backed by any epidemiological findings or animal experiments. From the point of view of preventive medecine it would be necessary to quantify the risks in order to establish priorities for protective measures. But it is just this that the Senate Commission declares to be impossible at present.

This year the Tübingen toxicologist Professor Remmer, who is a member of the Senate Commission and a zealous supporter of the inclusion of passive smoking in the MAK-List, published a paper in the 'Deutsche Medizinische Wochenschrift' in which tobacco smoke is described as the most dangerous noxious substance to man in the air we breathe. He had noticed that in many epidemiological studies the difference in the risk of lung cancer through smoking and through passive smoking was too small for the risk incurred through passive smoking to be plausible. To explain this evident discrepancy Professor Remmer based himself on some very arbitrarily selected literature in order to draw up a theory according to which active smoking may cause far less cancer than passive smoking. It is believed that certain compounds contained in the mainstream smoke induce enzymes which detoxify the carcinogenic substances. Whereas in the sidestream smoke, to which passive smokers are exposed, these compounds are only found in ineffectively weak concentrations. Therefore, in contrast to what happens in the case of active smoking, very small quantities of inhaled carcinogenics could become fully effective. This theory is not supported by any scientific findings. Interpretation has taken the place of findings, which stands the process of acquiring knowledge on its head, as has been noted by the Research Council on Smoking and Health in a letter to the editor of the 'Deutsche Medizinische Wochenschrift'.

The Driving Forces

Bearing in mind the many risks to health to which we are daily exposed, passive smoking, which is considered a non-problem by many scientists, takes up an astonishing amount of room in public discussion. The question arises as to what may be the reasons which, despite the factual situation, keep the discussion on passive smoking going, and render it ever more passionate. I should like to pinpoint some of these reasons as follows:

Environmental consciousness has considerably increased in the course of the past decade. Therefore successful efforts have been made to reduce air pollution in our large cities and industrial conurbations as well as at the place of work without, however, even nearly attaining the desired goal of nil-pollution. More attention is being paid to indoor air pollution to which tobacco smoke contributes to a considerable degree because of the wide-spread habit of smoking. Modern methods of chemical analysis make it possible to discover even the minutest quantities of noxious substances. Although this is far from telling us anything about their toxicological significance, a need to act is created because people believe that ever less pollution must lead to ever better health. They leave out of account the doctrine of Paracelsus, which says that "the dose makes the poison."

Responsible politicians interested in health issues are bound to act in the interests of the people entrusted to their care, as soon as they are "adequately certain" that passive smoking may lead to a health risk for non-smokers. They cannot afford to wait until "a line of sick people, invalids and dead bodies can be produced to prove that they have fallen victim to passive smoking" as it was expressed in a Bundestag Printed Matter of 1974. Since politicians can hardly themselves have the scientific training to assess the risks, they must rely on the knowledge of others. This offers lobbies a chance to influence health policy decisions in one way or another.

A pluralistic society such as ours has lobbies. And it is they who have by now removed the subject of passive smoking from scientific discussion and have put it on the political stage. It would be wrong to impute this to bad intentions. Inadequate or biassed occupation with the problem, or general insecurity with regard to scientific comprehension, are quite enough.

- There are certain branches of industry and their corresponding trade associations who seem to believe that the term occupational cancer has lost its raison d'être. So far as they are concerned lung cancer stems from smoking only, and in the case of a non-smoker, well then it is due to passive smoking. The trade unions would be well advised to discover the error of their ways in good time and to protect their members from its pernicious consequences.

- There are anti-smoking movements which, after years of guerilla warfare against smoking, have had to realise that smokers react with surprising indifference to reproaches of self-inflicted injury or being a nuisance to others. It is the aim of the anti-smoking movements to bring about a smoke-free society by the year 2000. The means to attain this end is the social ostracism of smoking. No argument is better for this purpose than to maintain that by their inconsiderate behaviour smokers endanger the health of their fellow-men.

- Certainly the cigarette industry would also have liked to intervene in the process of shaping public opinion. After all, 90% of the public by now believe that the harmfulness of passive smoking has been proved and is hardly less than that of active smoking. But the industry's chances are poor, since it has an economic interest in the matter, and has a reputation for greed into the bargain.

Tobacco Smoke in Enclosed Spaces

Tobacco smoke in enclosed spaces consists of a mixture of about 15/20% exhaled mainstream smoke and 80/85% sidestream smoke. The mainstream component is very different from the sidestream component. Both originate in the burning zone of the cigarette, but at different temperatures. Mainstream smoke is inhaled by the smoker and in part exhaled again. Sidestream smoke originates between the puffs taken by the smoker and is released directly into the room, where it is diluted. Mainstream and sidestream tobacco smoke in a room are composed of a gaseous and a particle phase. More than 90% of the weight is accounted for by the gaseous phase. Quantitatively significant compounds are: vapour, carbon dioxide, carbon monoxide, ammonia, aldehyde and nicotine. Tobacco smoke in the room contains mainly the same substances as the mainstream smoke. Table 1 shows the concentrations of main and sidestream smoke in the air of the enclosed space under approximately realistic conditions.

There does not at present exist any reliable marker for tobacco pollution in enclosed spaces. The reason for this is that the sidestream smoke from cigarettes, cigars and pipes differs from product to product, that smokers as individuals and as between individuals produce different amounts of main and sidestream smoke, and that tobacco smoke in the air rapidly changes its composition as it ages. In addition, air in an enclosed space often contains substances which do not stem from tobacco smoke, and in some cases this kind of pollution can be greater than that caused by the tobacco smoke. Nicotine seems to be the most suitable marker for tobacco smoke in an enclosed space; 95% of it is part of the gaseous phase and not of the particle phase as in the mainstream smoke. Nicotine occurs in the enclosed air only if in fact there has been smoking. Carbon monoxide and other substances are less suitable as markers. They can only be employed where the basic pollution has been established first.

Undiluted sidestream smoke contains larger quantities of some carcinogenic substances such as polycyclic aromatic carbohydrates and volatile N-nitroso-compounds than are contained in the mainsmoke stream. Accordingly, the carcinogenic potential of sidestream smoke could be a little greater than that of the mainstream smoke, given equal quantities of substance. In their 1967 test on the skin of mice Wynder and Hoffman found that an application of condensate from sidestream smoke caused more tumors than an application of condensate from mainstream smoke. The gaseous phase was wholly neglected in this experiment. The same working party carried out inhalation experiments with hamsters, but no histological results are yet available. Astonishingly enough, however, the animals treated with main- and sidestream smoke lived longer than the untreated control animals.

One problem in comparing the carcinogenic potential of main- and sidestream smoke lies in the fact that mainstream smoke is immediately inhaled whilst sidestream smoke ages when released into the air and thereby loses much of its toxic potential. It is not known to what extent this is also true for its mutagenic and carcinogenic potential. The one thing that is sure is that in the course of time its composition changes considerably because of dilution, evaporation, oxidation, other chemical reactions, and selective surface absorption. The few available comparative studies of main- and sidestream smoke, which were mainly carried out to measure mutagenic potential are either faulty or have produced contradictory results. Nevertheless, some scientists still insist that tobacco smoke in an enclosed space is more carcinogenic than mainstream smoke. This hypothesis is based on a comparison of fewer than 100 substances -- of the 3800 compounds identified in tobacco smoke, this is a very modest fraction. It leaves out of account both the very considerable dilution of sidestream smoke in the enclosed air and the ageing process.

As compared with former times, sidestream smoke to-day releases fewer mutagenic and carcinogenic substances since the smokers of modern cigarettes produce more mainstream and less sidestream smoke because of the halving of the nicotine and condensate content which has taken place over the years. The reason for this lies in the lower tobacco content in cigarettes and improved filter techniques. It is likely that the reductions reach up to 20%. The figures obtained with smoking-machines, which argue in favour of a disproportionately high release of carcinogenic compounds in the sidestream smoke do not reflect this development because smoking-machines simulate the smoking habits of the nineteen-fifties.

Studies undertaken so far show that the components of tobacco smoke are variously distributed in the main- and sidestream as well as in the indoor air. For that reason alone it is not possible to extrapolate from the risks of the smoker to those of the passive smoker.

Inhalation of Tobacco Smoke through Passive Smoking

Effects of passive smoking on health can be expected if the noxious substances thus inhaled are sufficient to overcome the physiological defence system of man. Only a little more than 10% of the particle phase of tobacco smoke is retained in the respiratory passages according to Hiller. Only part of this is resorbed, since the lungs have an effective cleansing mechanism. In contrast to this, something between 45% and 95% of the particle phase of the mainstream smoke is retained in the lungs of the smoker, this smoke being highly concentrated as compared with the tobacco smoke in the enclosed space. Of

the gaseous phase of tobacco smoke in the enclosed air, mainly those compounds are resorbed in the nose and throat area and the upper respiratory tracts, which are easily soluble in water and/or chemically highly reactive. They are substances such as: formaldehyde, acetaldehyde acrolein, acetone, ammonia, and possibly also nicotine, ozone and free radicals. Insoluble and not highly reactive compounds such as carbohydrate can indeed reach the alveolar space of the lungs, but their rate of retention is very low. The mainstream smoke contains the major part of carcinogenic compounds in the particle phase. Whether this is also true of tobacco smoke in an enclosed space is not known, though there are some indications that this may be so.

Table 1

Important substances of tobacco smoke in mainstream smoke (HSR) and sidestream smoke (NSR) of cigarettes in an enclosed air space under approximately realistic conditions.

Substance	HSR Quantity/ Cigarette	NSR	Concentration in enclosed space
Carbon monoxide (CO)	2-20 mg	46-61 mg	3,6-24 mg/m3 (3-20) ppm.
Nitrogen oxide (NO)	0,07-0,17 mg	1,6-3 mg	83-333 ug/m^3 (50-200 ppb)
Nitrogen dioxide (NO_2)	n.n.	0,16 mg	19-132 ug/m^3 (10-70 ppb)
Ammonia (NH_3)	50 ug	5300-8500 ug	100-450 ug/m^3
Cyanide (HC)	150-550 ug	100-250 ug	10-120 ug/m^3
Formaldehyde	20-90 ug	450-1500 ug	20-100 ug/m^3
Acetaldehyde	18-1400 ug	2400 ug	400-500 ug/m^3
Acrolein	25-140 ug	925 ug	15-25 ug/m^3
Nicotine	0,5-2 mg	3-4 mg.	20-100 ug/m^3
Phenol	10-130 ug	270-320 ug	< 1-20 ug/m^3
Benzol	10-100 ug	488 ug	5-16 ug/m^3
Volatile Nitrosamines			
NDMA	0,2-20 ng	155-398 ng	5-70 ng/m^3
NDYR	2,4-29 ng	7-150 ng	1-5 ng/m^3
Nitrosamines specific to tobacco			
NNN	0,20-5,5 ug	0,15-6 ug	< 1-6 ng/m^3 3)
NNK	0,1-4,2 ug	0,2-0,8 ug	< 2-11 ng/m^3 3)
Benzo(a)pyrene	10-50 ng	25-103 ng	3-25 ng/m^3
Cadmium	100 ng	430-720 ng	9-31 ng/m^3
Particles (TPM)	5-30 mg	20-50 mg	0,1-0,5 mg/m^3

Attempts have been made to quantify, with the aid of various biochemical markers, the absorption of tobacco smoke through smoking and passive smoking. A reliable marker should be tobacco-smoke-specific and should, in resorption, behave as those substances which entail the greatest risk to health. Compounds which are resorbed in the nose and throat area should therefore, not be used to assess the risks of lung cancer. Biochemical markers which would answer these requirements are not yet known. The most suitable seems to be cotinine, a nicotine metabolite. Nicotine and cotinine in body fluids prove exposure to tobacco. However, it is difficult, or even impossible, to quantify the exposure. In passive smoking nicotine acts only partly like the mutagenic and carcinogenic compounds of the particle phase. Tobacco smoke in enclosed air contains it in the gaseous phase, as has been pointed out, and not in the particle phase as is the case with mainstream smoke. Nicotine occurs as a base and is more quickly resorbed in this form than the protonised nicotine of the mainstream smoke. To some extent this already happens in the nose and throat area and the upper respiratory tracts. Nicotine, the half-life of which is short at 30 minutes is also differently metabolised as between one individual and another. In passive smokers the half-life of cotinine, which is 15 to 25 hours in smokers, is further reduced. The cotinine level in the serum, and the nicotine and cotinine excretion in urine are considerably influenced thereby, so that they are only of limited value as a measure for the absorption of tobacco smoke. In no circumstances should such data be considered suitable for the assessment of the lung-cancer risk. This is true even where they may show a correlation with tobacco pollution, as has emerged from some experiments. Nonetheless some authors maintain the view that passive smokers inhale up to 1% of the amount of tobacco smoke inhaled by smokers and conclude therefrom that they are exposed to about 1% of the risk to which smokers are exposed. Table 2 shows the nicotine and cotinine concentrations in the body fluids of smokers and passive smokers.

Alongside nicotine, carboxyhaemoglobin and thiocyanate contained in serum are also used to measure the exposure of non-smokers to tobacco. They are however even less suited than nicotine or cotinine to establish the exposure to tobacco. Carbon monoxide which is formed in the body's own metabolism normally leads to an approximately 0.7% concentration of carboxyhaemoglobin. As a rule no increase, or only a small increase, is found in passive smokers. It is only under extreme conditions and after an exposure to tobacco of several hours that a carboxyhaemoglobin value of 2% can be attained. Thiocyanate stems from hydrogen cyanide which also occurs in tobacco smoke. Both carbon monoxide and hydrogen cyanide (or cyanide ions) are tobacco-smoke unspecific and can be found in the air or in food, and also in concentrations which can be much higher than those found in tobacco smoke in enclosed spaces.

Groups studied/Exposure	N	Result	Literature
Clinical Staff			
- not exposed (a.m.)	30	Nicotine in urine: 7.5 ± 8.3 ng/ml	Feyerabend et al 1982
- exposed (a.m.)	26	Nicotine in urine: 21.6 ± 28.8 ng/ml	
- cigarette smokers (average inhalers)	32	Nicotine in urine: 1343.4 ± 1699.8 ng/ml	
Patients and Clinical Staff			
- not exposed	22	Cotinine in urine: 2.0 ng/ml (Median)	
- exposed	199	Cotinine in urine: 6.0 ng/ml (Median)	
- Cigarette smokers	131	Cotinine in urine 1645.0 ng/ml (Median)	Wald et al. 1984
Husbands			
- non-smoking wife	101	Cotinine in urine: 8.5 ± 1.3 ng/ml	Wald and Ritchie 1984
- smoking wife	20	Cotinine in urine: 25.2 ± 14.8 ng/ml	
Clerical Staff			
Blood samples at 11.30 and 19.45 (in between, two hours in a smoke-filled bar)	7	11.30 / 19.45 Nicotine in Plasma 0.8 / 2.5 ng/ml Nicotine in urine 10.5 / 92.6 ng/ml Cotinine in Plasma 1.1 / 7.3 ng/ml Cotinine in Saliva 1.5 / 8.0 ng/ml Cotinine in urine 4.8 / 12.9 ng/ml	Jarvis et al. 1983
Ambulant patients			
- non-smokers, not exposed	46	Nicotine in plasma: 1.04 ng/ml Nicotine in urine : 3.87 ng/ml Cotinine in plasma: 0.82 ng/ml Cotinine in saliva: 0.73 ng/ml Cotinine in urine: 1.55 ng/ml	Jarvis et al. 1984
- non-smokers, exposed	54	Nicotine in plasma: 0.77 ng/ml Nicotine in urine: 12.11 ng/ml Cotinine in Plasma: 2.04 ng/ml Cotinine in saliva: 2.48 ng/ml Cotinine in urine: 7.71 ng/ml	Russel 1987
- Smokers	94	Nicotine in plasma: 14.6 ng/ml Nicotine in urine: 1749.9 ng/ml Cotinine in plasma: 275.2 ng/ml Cotinine in saliva: 309.9 ng/ml Cotinine in urine: 1391.0 ng/ml	
Staff			
- Clerical staff not exposed	20	Cotinine in plasma: 5.2 ± 1.5 ng/ml Cotinine inurine : 8.3 ± 6.7 ng/ml	
- Waiters, Waitresses exposed	26	Cotinine in plasma: 10.0 ± 4.0 ng/ml Cotinine in urine: 56 ± 37 ng/ml	Husgafvel - Pusiainen et al. 1987
- Smokers	22	Cotinine in plasma: 246 ± 91 ng/ml Cotinine in urine: 1578 ± 765 ng/ml	

Table 2: Nicotine and cotinine in body fluids of non-smokers and not exposed to tobacco under real conditions

Groups studied/Exposure	N	Result			Literature
Clinical Staff					
- not exposed (a.m.)	30	Nicotine in urine:	7.5 ±	8.3 ng/ml	Feyerabend et al 1982
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		Cotinine in Plasma	1.1	7.3 ng/ml	Jarvis et al. 1983
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		Nicotine in urine:	12.11 ng/ml		
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		Cotinine in saliva:	2.48 ng/ml		
		Cotinine in urine:	7.71 ng/ml		
- Smokers	94	Nicotine in plasma:	14.8 ng/ml		
		Nicotine in urine:	1749.9 ng/ml		
		Cotinine in plasma:	275.2 ng/ml		
		Cotinine in saliva:	309.9 ng/ml		
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Table 2: Nicotine and cotinine in body fluids of non-smokers and not exposed to tobacco under real conditions

According to a study carried out by the Bremen Institute for Preventive Research and Social Medecine we must assume that the total exposure of non-smokers lies in the private sphere to more than 60%, the main cause being smoking spouses. However, in working men and women exposure at the place of work also plays an important part. According to a study by Letzel and Johnson the daily exposure to tobacco smoke amounts to between 1 to 2 hours for men and a little less for women. The duration of exposure fluctuates according to age and sex.

Epidemiological Findings - Lung Function in Adults

To date eight epidemiological studies are available, of which four point to a deterioration of lung function as a result of passive smoking. One of them is the paper by White and Froeb referred to earlier on, which does not attain scientific standards but is nevertheless the one most frequently quoted as evidence of lung damage through passive smoking. In the four other studies, including one from the Federal Republic, no influence of passive smoking on lung function was found. The problem with studies of this kind is that there are numerous environmental factors which can impair lung function and that it is difficult or even impossible to isolate one single cause. This is the view also taken in the 1986 Report of the Federal Environment Office.

Lung Function in Children

There exist at least twenty epidemiological studies, all carried out in a similar manner, in which the influence of parental smoking on the lung function of children is examined. Thirteen of them conclude that smoking by parents, especially by mothers, impairs the children's lung function. The differences between such children and others whose parents did not smoke were small and varied between less than 1% and 8%. In an analysis presented on the occasion of the "Indoor Air Conference '87" in Berlin, Professor Witorsch of the Virginia Commonwealth University (USA) doubted even this order of magnitude. He pointed out that in all these studies the socio-economic status of the parents and their children had been either left out of account altogether, or had been only very superficially taken into consideration. The socio-economic status however is related to smoking as well as to other factors which influence the measurement of children's lung function. Some of these are different attitudes to learning and an absence of motivation, which can have a negative effect on the test result. Moreover it is known that, as compared with non-smokers, smokers inhabit on the whole a lower socio-economic status which implies less favourable housing so far as area, size and equipment of accommodation are concerned, and with a less health-conscious life-style of the family with regard to nutrition, sports and other habits and

attitudes. Here again it is virtually impossible in a statistical analysis to exclude all these 'confounding factors' as potentially contributory causes for a deterioration in the lung function and the appearance of pulmonary symptoms. In fairness it ought therefore to be conceded that the question as to the extent to which passive smoking plays a part in all this has not yet been satisfactorily answered. The suspicion however remains.

Coronary Heart Diseases

So far a total of 7 epidemiological studies are known which deal with the possible influence of passive smoking in the genesis of coronary heart diseases. In his above-mentioned study Hirayama found that in non-smoking wives of smokers of more than 20 cigarettes per day, there was a relative risk of 1.35. He did not, however, standardise other coronary risk factors such as hypertension or hyper-cholesterol-aemia. His observation is the more astonishing as in Japan smoking as such is of only limited significance for coronary heart disease. Garland and collaborators carried out a case-control study on wives of smokers and ex-smokers and established a relative risk of 2.7, which is marginally significant. Not to mention a few methodological problems which arise from this study, it is most remarkable that 15 of the 19 deaths were of wives of ex-smokers. This contradicts the findings relating to smokers, whose relative risk after giving up smoking declines rapidly and after a few years becomes the same as that of non-smokers. Three of the remaining studies tend towards establishing a link between passive smoking and coronary heart disease; two, including that by Garfinkel which is comparable to that by Hirayama, do not do so. The value of this study is doubted even in the mainly politically-motivated report of the American Surgeon General. Too many problems of method seem unanswered and the doubts concerning the plausibility of the results obtained so far are evident. The risk of death through a myocardial infarct is two to three times higher in our Western societies for smokers than for non-smokers.

It seems that smoking combines with other existing risk factors rather than being an independent risk factor itself. Nicotine and carbon monoxide which in theory are supposed to be responsible for the increased coronary risk to smokers cannot be potential causes as passive smokers absorb them only to a very small extent. This being so, Professor Schmähle was right when on one occasion he asked what could be the 'devilish substance' in tobacco smoke which could bring about such an increased coronary risk in indoor air.

Lung Cancer

In at least eight cohort-studies and 50 case-control studies a significant correlation was established between smoking and lung cancer. The relative risk of lung cancer to male smokers

of one to ten cigarettes per day covers a span from 1.9 to 4.6. Where more than 25 cigarettes are smoked it rises to between 4.6 and 25.1. Since indoor tobacco smoke also contains mutagenic and carcinogenic substances -- though in much smaller quantities than in the mainstream smoke inhaled by the smoker -- the question whether passive smoking may bring about an increase in the risk of lung cancer is perfectly legitimate. As in the case of smoking, epidemiological studies are the proper means to discover any link that may exist. But because the risk to be expected is much smaller, these studies must be planned and carried out as faultlessly as possible. Otherwise we are likely to get artefacts rather than results.

So far three cohort studies are available, of which one does not permit any conclusion to be drawn because of the small number of cases: only six non-smoking men and eight non-smoking women. The American paper by Garfinkel does not present any link between passive smoking and lung cancer. In contrast, Hirayama believes, in the paper already referred to, that he can prove the existence of a significant dose-response ratio. Because mass studies are much superior to case control studies so far as the force of their evidence is concerned, and because Hirayama's findings have so far provided the strongest arguments in favour of a cancer risk through passive smoking, I should like to take a closer look at his work. At a symposium a few weeks ago in Tokyo, Professor Uberla, a former chairman of the Federal Health Office pointed out the following shortcomings of the paper in the presence of Dr. Hirayama:

- The paper was not planned in order to test the hypothesis that passive smoking is, or is not, associated with lung cancer;

- The group examined was not representative of Japan so that there may have been a bias in selection;

- The indicator for exposure to passive smoking -- being married to a smoking husband -- is neither reliable nor valid and it is not specific;

- The indicator for the potential consequences of passive smoking -- lung cancer as the cause of death in the death certificate -- is neither reliable nor valid;

- Various 'confounding factors' such as exposure at place of work, general air pollution, differences in nutrition, the type of medical treatment, etc., were not taken into account;

- A possible bias in the classification of women as non-smokers was not excluded, so that it may be assumed that there were some smokers amongst the non-smokers;

- Almost nothing is known about the 200 deaths reported. There is not a single medical history available and histological findings and reports on autopsies are available in only 11.5% of the cases.

In their re-analysis of Hirayama's data, Uberla and Ahlborn found that the conclusions drawn by Hirayama on the basis of the data published so far are not cogent. When adjusted to the normal age-distribution in Japan the risk of lung cancer due to passive smoking disappeared altogether. In his address in Tokyo, Professor Kilpatrick of the Virginia Commonwealth University (USA) unreservedly agreed with this assessment.

Apart from the cohort studies we now have 19 case control studies. The great majority of these find a relative risk of > 1.0 for lung cancer through passive smoking. The risk-increase which reaches a maximum of 3.23 is significant in only a small number of studies, and a dose/response ratio is established only rarely. Case control studies in which relative risks of 2 or less, i.e. low risk associations, are to be discovered must be faultlessly planned and carried out if they are to allow any conclusion to be drawn at all. Otherwise an increased risk found could be due to a bias or confounding factor. It does not really matter whether such a risk increase is significant or not. After all, significance is no more than a yardstick for the probability of the fortuitously obtained figure being really different from the one expected, it being assumed a priori that the classification of cases is not governed by additional factors.

The first Report by the American Surgeon General, the 1964 Terry-Report, describes the criteria to be met by epidemiological studies in order that a causal link may be assumed. In his review paper "Lung Cancer from Passive Smoking: Hypothesis or Convincing Evidence?" just recently published in the 'International Archives of Occupational and Environmental Health', Professor Uberla notes that in the epidemiological studies published so far these criteria have not, or only partly, been met. A similar conclusion was arrived at by Professor Wynder of the New York American Health Foundation in his address in Tokyo a few weeks ago. The following must be taken into consideration when a causal link is examined:

- At a relative risk of <3 or even <2 the strength of the association is small in all studies. Therefore it would have been particularly important carefully to avoid possible mistakes of method, which was certainly not done. On the other hand there can be no doubt that even a slightly increased risk, if real, would be of great importance from the point of view of public health, given the widespread phenomenon of passive smoking.

- As to the concordance of results within a study or between studies, many questions remain unanswered. Thus not all studies establish a link between passive smoking and lung cancer. In some cases such a link can be shown only through an analysis of sub-groups. In some studies the adenocarcinoma-rate only seems to have increased whereas in others it is only the rate of epithelium-carcinoma.

- Nor is the specificity of association, apparent in the relationship between the exposure and its consequences, properly assured. Neither the measure of exposure -- usually obtained by asking about the spouse's smoking habits -- nor the diagnosis of lung cancer are valid or specific in the light of available experience. In the light of Garfinkel's case-control study Wynder showed how difficult it is to carry out questioning correctly. If the questions were answered by the patient himself, the relative risk came to 1.0, if the spouse answered, it was 0.92, and if the replies came from either daughter or son the figure was 3.19, and when acquaintances were asked, it dropped to 0.77. Despite all these contradictions Garfinkel's study is regarded by some as a further proof of the risk of lung cancer through passive smoking because of its overall significantly-increased relative risk of 2.1. In fact however, in view of the problems highlighted, it would rather seem to prove the opposite. According to Lee the possibility of misclassification constitutes the greatest problem for epidemiological studies of passive smoking, and especially for case control studies. Misclassification quite simply has its origin in wishful thinking to which patients, relatives and researchers may be prone. Because of the human need to find a cause for a blow of fate the former tend to overestimate passive smoking as a possible cause, and the latter would like to see a preconceived opinion confirmed. Garfinkel and collaborators in fact point to the possibility of misclassification after they were compelled to find that about 40% of all patients registered as non-smokers in their sick-reports were in fact smokers. Lee calculated that a small percentage of women smokers erroneously classified as non-smokers was sufficient to falsify results and to show an increased risk of lung cancer through passive smoking.

- Problems arise with regard to time relationships. Though all epidemiological studies show that differing periods of latency precede the genesis of lung cancer due to exposure to passive smoking. But there is hardly one study in which passive smoking during childhood or youth has been properly taken into account. Since according to Doll and Peto the period of exposure in terms of life-years seems to be more important than the magnitude of the dose, passive smoking extending from childhood through adolescence into adult age is supposed to be particularly

disadvantageous. Only Correa and collaborators made an effort to cover childhood smoking. They found that the relative risk of lung cancer was 1.0 where the father smoked and 1.66 where the mother did. This increased risk was significant only for male patients and did not apply to female patients. A further argument against the importance of passive smoking as a cause of lung cancer is proferred by Wynder: the risk of lung cancer in non-smokers should in fact have risen over the past decades in parallel with the greater frequency of lung cancer in smokers if passive smoking were a causal factor. This is however not the case.

- In some studies a significant dose/response ratio was found, such as in the cohort study by Hirayama and in the Greek case control study by Trichopoulos. But Uberla describes this latter as a text-book example for all those mistakes which should be avoided at all cost in a case control study. There are several studies in which there is no pointer to a dose/response ratio.

- The case for biological plausibility is similar to that of the epidemiological findings. In both cases there is more than enough reason for doubt. First, one may well wonder whether a fraction of the substances inhaled by smokers can really trigger off a relatively high risk of lung cancer through passive smoking. Epithelium carcinoma (Plattenepithelkarzinom) which according to some studies is supposed to be more than normally frequent in passive smokers begins in cilia-bearing cells which must have undergone metaplastic change. Auerbach and collaborators have shown that the preliminary stages of malignant changes in the bronchial tracts of passive smokers, namely metaplasia and dysplasia can hardly be proved and that the cilia of the cells seem to remain intact. It is likely that no preliminary stages of bronchial carcinoma can be detected because passive smoking does not overload the physiological defence system of the lungs. There is much that argues in favour of this view. It is, however, not proved.

  Since 1986 one particular form of evaluating epidemiological studies on passive smoking has gained great importance: it is known as meta-analysis and amounts to the merging of all - or at least most - presently available studies for the purpose of increasing the number of cases and thereby to arrive at a more reliable conclusion. The first analysis of this nature led Professor Wald of St. Bartholomew's Hospital, London, to conclude that the relative risk of lung cancer for passive smoking is 1.30 and thus significantly increased. Wald's paper was regarded as proof of the risk of lung cancer to passive smokers by both the American Surgeon General and the National Academy of Sciences. Despite the esteem in which the authorities hold that paper there are

considerable doubts as to whether it is justifiable to merge the results of epidemiological studies of different quality and to evaluate them jointly. At the end of the day the conclusive value of a meta-analysis very clearly declines with the number and magnitude of the errors contained in the studies upon which it is based. Bearing this in mind, Letzel and Uberla carried out a further meta-analysis based only on those epidemiological studies which meet minimal standards of scientific quality. On the basis of twelve relevant studies they reached the conclusion that if the Trichopoulos-study is taken into account the relative risk amounts to 1.12, and if it is not, the figure declines to 1.08. That risk-increase however is not significant and remains within the limits of 'statistical smoking'.

Toxicology of Passive Smoking

In view of the evident difficulties epidemiologists encounter in helping to find out whether there is a link between passive smoking and lung cancer, it is not to be wondered at that the toxicologists have been giving more and more attention to the subject. The findings established so far were discussed in 1986 at a symposium in Essen and in 1987 at congresses in Berlin and Tokyo. The results, most of which were obtained in more or less controlled chamber-experiments are in part contradictory. Persons exposed to tobacco smoke most frequently complain about irritation of the mucus membranes, for which mainly substances contained in the gaseous phase, but probably also in the particle phase, are responsible. Subjective sensations of feeling ill and bad smell are quoted as additional nuisances. According to Professor Winneke of the Institute for Air Hygiene and Silicosis Research of Düsseldorf University early difficulties of this nature occur when the concentration of tobacco smoke corresponds to 5 ppm CO and not, as alleged in an earlier study by Weber and collaborators, at 2 ppm CO. Whereas irritations increase with the duration exposure, the other effects are complained of only during the initial ten to fifteen minutes.

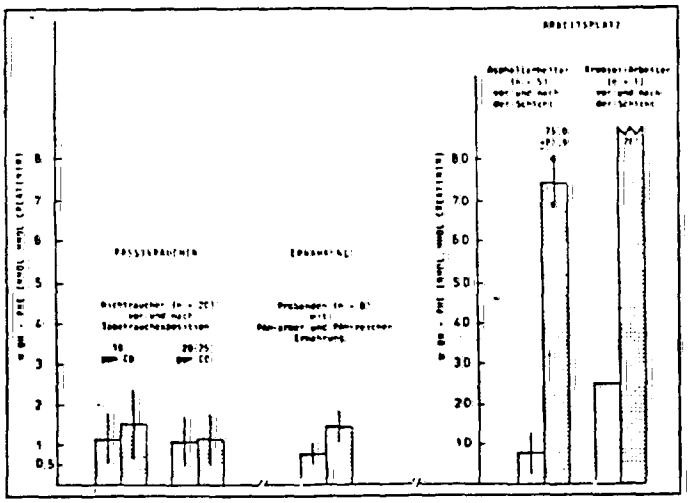
Nicotine, cotinine and thiocyanate in body fluids as well as carboxyhaemoglobin merely show that there has been exposure to tobacco smoke. In order to cover the long-term effects of exposure to tobacco smoke it would seem necessary to examine the absorption and the effect of compounds with genotoxic qualities. Below, the results are presented of a number of experiments which deal with this problem.

Phenanthrene is part of the group of polycyclic carbohydrates (PAH) and is contained in cigarette smoke, diesel exhaust fumes and also in roast pork. Hydroxyphenanthrenes are products of the metabolism of phenanthrene and are rightly considered to be

markers for the absorption of PAH. We were able to show that the excretion of hydroxyphenanthrene in urine does not increase after an 8-hour exposure to tobacco smoke, irrespective of whether the concentration at 10 ppm CO is medium or very high at 20 to 25 ppm CO. (Graph 1). The excretion of hydroxyphenanthrene changes significantly if, after a diet low in PAH, one is provided which is high in PAH. Extremely high excretion of hydroxyphenanthrene is found in workers exposed to high PAH concentrations at work. Data established in co-operation with Professor Grimmer from the Biochemical Institute for Environmental cancer in Hamburg show how widely the PAH impact fluctuates and how secondary the role which passive smoking plays therein.

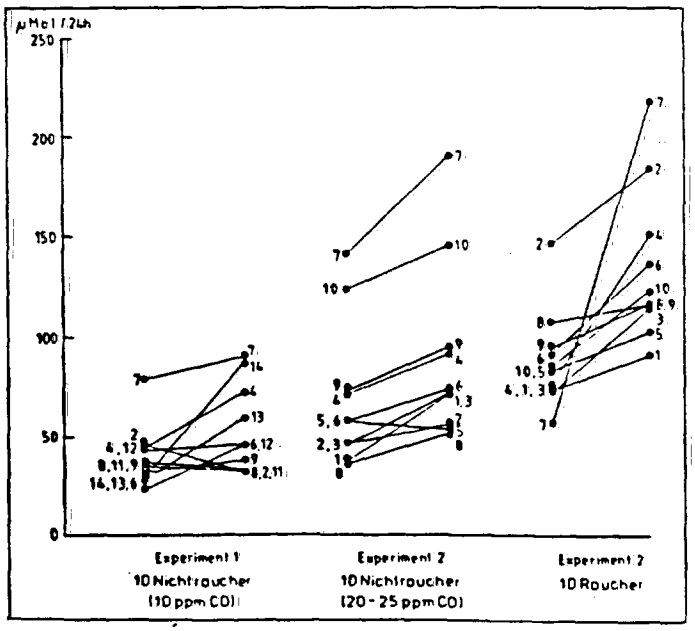
Mercapturic acids (thioethers) are the detoxification products of many electrophile, and thus potentially mutagenic and carcinogenic, substances. Their genesis is catalysed by the glutathion-S-transferase-system and their rate of excretion in urine can be used to measure the impact of these compounds. The excretion of mercapturic acids rises slightly when a non-smoker has been exposed for 8 hours to a tobacco smoke concentration of 10 ppm CO and increases further when this is doubled (Graph 2). As compared with non-smokers, the thioether-excretion is still higher than normal in smokers after an abstinence of 36 hours and, after ten to 20 cigarettes have been smoked, it increases more vigorously than in passive smokers. The higher excretion of thioethers after passive smoking was, by the way, described for the first time and was probably discovered only because the diet of the test persons had been strictly controlled over a period of several days. The results of the experiment carried out in co-operation with Professor Sorsa of the Institute of Occupational Health in Helsinki confirm the view that through passive smoking electrophile substances are absorbed and detoxified. How effective this detoxification is, requires further study.

Mutagenic and carcinogenic substances are excreted in urine if they neither react with macromolecules in the organism, such as DNA, nor are detoxified in metabolism through the various protective enzyme systems. They can be detected in urine through the Ames-Test. In our experiment we found no significant increase in mutagenic activity in passive smokers either after a medium (10 ppm CO) or a high eight-hour exposure to tobacco smoke (20 to 25 ppm CO) (Graph 3). With one exception our results agree with those of other authors so far as the extent of mutagenic activity is concerned. Professor Norpoth's working party of the Institute of Hygiene and Social Medecine of Essen University found an increase in passive smokers which corresponded to that of smokers of four to five cigarettes. The reason for this different result is not at present known and needs to be discovered. Our results suggest that in contrast to smoking, passive smoking leads to the absorption of too few mutagenic or carcinogenic substances for



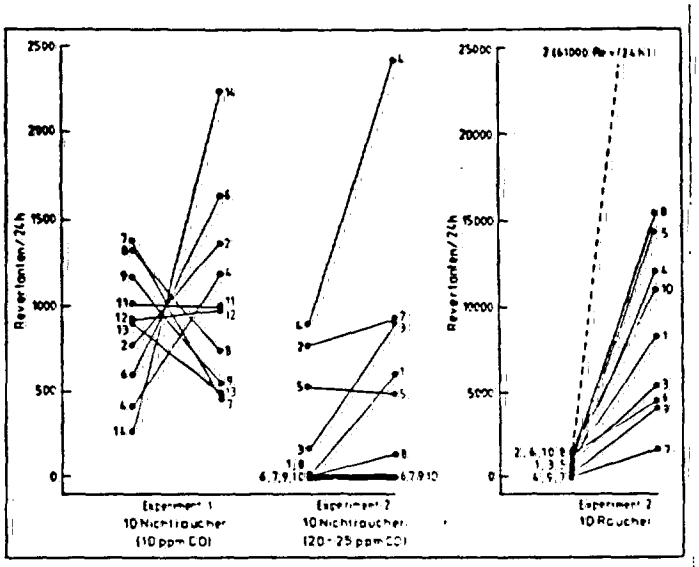
Graph 1

Hydroxyphenanthrene excretion in urine following PAH absorption during medium (10 ppm CO)-to-heavy (20-to-25 ppm CO) tobacco smoke exposure, during nutrition both poor and rich in PAH and at selected workplaces.



Graph 2

Thioether excretion in the urine of non-smokers before and after eight-hour-long medium (10 ppm CO)-to-heavy (20-to-25 ppm CO) tobacco smoke exposure, compared with that of smokers.



Graph 3

Mutagenic activity in the urine of non-smokers before and after eight-hour-long medium (10 ppm CO)-to-heavy (20-to-25 ppm CO) tobacco smoke exposure, compared with that of smokers.

them to be detected with the Ames-Test in urine. It is however just as possible that these substances can be effectively detoxified in passive smokers through the cellular glutathion-S-transferase-system and other enzymes, which does not seem to be possible in the case of smokers because of the overload with which their metabolism is charged.

Under the impression of the results of the symposium on "Experimental Toxicology on Passive Smoking" in Essen Professor Gostomczyk made the following comment: "Taking into account the results of the Essen symposium we may say that toxicologists have so far no more than epidemiologists rendered more probable the existence of a link between passive smoking and injuries to health." Our findings should be interpreted on the same lines.

Conclusions

Tobacco smoke indoors contains toxic, mutagenic and carcinogenic substances which are inhaled by non-smokers. The concentrations are all low. There does not, at present, exist a marker for indoor tobacco smoke. The reason for this is that the composition of tobacco smoke differs according to the product from which stems, and that it is subject to constant quantitative and qualitative change through ageing. It is almost always mixed with substances of another origin, the concentration of which is frequently higher than that due to tobacco smoke. However, nicotine, which is specific to tobacco smoke, can be used to provide qualitative proof of indoor air pollution through tobacco smoke.

The particle phase of tobacco smoke is retained in the lungs at a rate of a little more than only 10% after inhalation. It may be assumed that a considerable part of it is not absorbed by the organism but is removed from the respiratory passages through the cleansing mechanism of the lungs. Reactive compounds of the gaseous phase and/or such which are easily soluble in water are largely resorbed in the nose and throat area and the upper respiratory passages. This is to some extent also true of nicotine, the metabolism of which varies from individual to individual, and is mainly broken down into cotinine. The presence of nicotine and cotinine in body fluids confirms exposure to tobacco smoke. It is hardly possible to quantify the impact of tobacco smoke on the basis of the nicotine or cotinine concentration in body fluids. Such a procedure is hampered by the great difference between indoor tobacco smoke and mainstream cigarette smoke, the quick quantitative and qualitative changes to which indoor tobacco smoke is subject, the specific physico-chemical qualities of nicotine, and the individual differences in the metabolism of nicotine. Carbon monoxide and thiocyanate are further, but unspecific, markers for the absorption of tobacco smoke.

Epidemiological studied carried out so far and which point to a link between passive smoking and lung cancer as well as other diseases are tainted with so many errors - when critically considered - that they cannot be regarded as confirming any danger to health due to passive smoking. Problems in measuring exposure to tobacco smoke, in eliminating misleading factors such as misclassifications or 'confounders', and in the diagnosis and typification of lung cancers, have on the whole not been resolved. In the opinion of many scientists the epidemiological methods available to-day are probably inadequate to discern any risk to health through passive smoking, if indeed there is such a risk.

Since epidemiology has so clearly failed to establish whether there is a risk to health through passive smoking, it is not to be wondered at that by now toxicologists have taken the matter up. At present they are the strongest upholders of the theory of harmfulness to health, especially of the danger of cancer through passive smoking. They rightly assume that through passive smoking mutagenic and carcinogenic substances are inhaled, albeit in weak concentrations. They further assume, probably wrongly, that there is no threshold for cancerogenic substances, right down to the single molecule. These two assumptions together of necessity lead them to the conclusion that the risk of lung cancer - and probably of other cancers too - is increased through passive smoking, however small that increase may be. A linear extrapolation from tobacco-pollution through smoking to tobacco-pollution through passive smoking, which is made as a result of these assumptions and does not seem justified in the light of the known facts, leads to a similar assessment.

The question whether passive smoking causes lung cancer becomes the more of a political problem the more it is emotionalised in public discussion and the less science is able to provide an answer. For the present we can only say that danger to health is theoretically a possibility but has by no means been scientifically proved. Politicians interested in health affairs want to know whether a risk to health is probable. My answer would be "No", but I realise that we may yet have to wait a long time for the final word.

Literature can be obtained from the author.

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